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(54) Title: NASAL DELIVERY OF APOMORPHINE

(57) Abstract: Intranasal delivery methods and compositions for the delivery of dopamine receptor agonists are provided which are effective for the amelioration of erectile dysfunction in a mammal without causing substantial intolerable adverse side effects to the mammal. Nasally administered compositions for treating male erectile dysfunction in a mammal are also provided which include a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its solubility and/or stability.

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NASAL DELIVERY OF APOMORPHINE

BACKGROUND OF THE INVENTION

The present invention relates generally to intranasal delivery methods and dosage forms. More particularly, methods and dosage forms for the safe and reliable intranasal delivery of apomorphine to ameliorate erectile dysfunction in a mammal are provided.

Apomorphine is a potent dopamine receptor agonist which has a variety of uses. For example, it has been effectively used as an adjunctive medication in the treatment of Parkinson's disease which is complicated by motor fluctuations (T. van Laar et al., *Arch. Neurol.*, 49: 482-484 (1992)). In particular, apomorphine has been used for relieving "off-period" symptoms in Parkinson patients with such response fluctuations. In the study by van Laar et al., the intranasally applied apomorphine used to achieve the results reportedly included an aqueous solution of apomorphine hydrochloride (HCL) at a concentration of 10 mg/ml. This formulation is also used for parenteral application and is published in different Pharmacopeia's.

Also, U.S. Patent No. 5,756,483 issued to Merkus (hereinafter "the '483 patent") which is hereby incorporated by reference, discloses the intranasal delivery of a variety of compositions, including apomorphine in combination with a cyclodextrin and/or a polysaccharide and/or a sugar alcohol for treating Parkinson's disease. The '483 patent, however, discloses very narrow dosage ranges of 0.1 to 2 mg of apomorphine per nostril which is specifically tailored for the amelioration of the "off-period" symptoms of Parkinson's disease.

Further, U.S. Patent No. 5,770,606 issued to El-Rashidy et al. (hereinafter "the '606 patent"), which is hereby incorporated by reference, discloses the delivery of apomorphine in a sublingual dosage unit for alleviating psychogenic impotence or

erectile dysfunction with no substantial undesirable side effects. The '606 patent further includes results from a study conducted by the inventors on the effect of apomorphine delivered intranasally on erectile dysfunction. The study suggested that intranasal delivery of apomorphine at concentrations of 2.5 mg to 3.5 mg was effective for eliciting an erection in patients suffering from erectile dysfunction, however, since the study participants suffered extensive and serious side effects including hypotension, nausea, vomiting, impaired vision, diaphoresis and ashen coloring, it was concluded that intranasal delivery of apomorphine to treat erectile dysfunction was insufficiently safe and reliable to be a viable commercial product.

Accordingly, it is one of the purposes of this invention, among others, to provide a safe and reliable intranasal delivery system for apomorphine that ensures delivery of therapeutic amounts of the drug into the bloodstream which is fast acting, easily administered and causes no substantial adverse side effects.

SUMMARY OF THE INVENTION

It has now been discovered that this and other purposes can be achieved by the present invention, which provides for a method for ameliorating male erectile dysfunction in a mammal. This method includes the nasal administration of a dopamine receptor agonist to the mammal before, during or after sexual activity in an amount sufficient to induce an erection without inducing substantial intolerable side effects in the mammal. Preferably, the dopamine receptor agonist is apomorphine.

The present invention also provides for a pharmaceutical composition for treating male erectile dysfunction in a mammal without causing substantial intolerable adverse side effects that includes a therapeutically effective amount of a dopamine receptor agonist in combination with a nasal delivery system. Preferably, the dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof and even further preferably, the dopamine receptor agonist is apomorphine. The chemically modified

equivalents of apomorphine preferably include a pro-drug. Further, it is preferable that apomorphine is dispersed in an aqueous or non-aqueous formulation.

In addition, the nasal delivery system of the pharmaceutical composition can include a buffer to maintain the pH of the dopamine receptor agonist, a pharmaceutically acceptable thickening agent and a humectant. The pharmaceutical composition can further include one or more pharmaceutical excipients and even further include a pharmaceutically acceptable preservative.

The buffer of the nasal delivery system can be selected from the group including acetate, citrate, prolamine, carbonate and phosphate buffers.

The thickening agent of the nasal delivery system can be selected from the group including methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

The humectant of the nasal delivery system can be selected from the group including sorbitol, glycerol, mineral oil, vegetable oil and combinations thereof.

The present invention also provides a method of treating erectile dysfunction in a male mammal including nasally administering a pharmaceutical composition including a therapeutically effective amount of a dopamine receptor agonist in combination with a nasal delivery system wherein the pharmaceutical composition does not cause substantial intolerable adverse side effects in the mammal.

The present invention also provides for a nasally administered pharmaceutical composition that includes a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain its pH, a pharmaceutically acceptable thickening agent and a humectant, wherein said nasally administered pharmaceutical composition does not cause substantial intolerable adverse side effects when

administered to a mammal. The dopamine receptor agonist of the nasally administered pharmaceutical composition is selected from the group including apomorphine, chemically modified equivalents and pharmaceutical salts thereof. It is further preferable that chemically modified equivalents of apomorphine include a pro-drug.

The present invention also provides for a method of treating impotence and male erectile dysfunction in a human in need of such treatment including administering to a nasal membrane of the human an effective amount of a nasally administered pharmaceutical composition including a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain its pH, a pharmaceutically acceptable thickening agent and a humectant, wherein the nasally administered pharmaceutical composition does not cause substantial intolerable adverse side effects when administered to the human.

Another preferred method of the present invention also provides for treating male erectile dysfunction in a mammal without causing substantial intolerable adverse side effects. This method includes administering into a nasal cavity of the mammal a therapeutically effective dosage of a dopamine receptor agonist in combination with a nasal delivery system. The nasal delivery system includes a pharmaceutically acceptable buffer, a thickening agent and a humectant. The dopamine receptor agonist is selected from the group including apomorphine, chemically modified equivalents and pharmaceutical salts thereof. Preferably, chemically modified equivalents of apomorphine include a pro-drug.

Another preferred method of the present invention is a method for administering a therapeutically effective amount of a dopamine receptor agonist to a mammal through a nasal membrane without causing substantial intolerable adverse side effects. This method includes delivering to the nasal membrane of a mammal a dopamine receptor agonist dispersed in a nasal delivery system which includes a pharmaceutically acceptable buffer, a thickening agent and a humectant. Preferably,

the dopamine receptor agonist is effective for the treatment of male erectile dysfunction in a mammal.

The present invention also provides for an intranasal dosage unit for treating impotency or erectile dysfunction in a mammal which does not cause substantial intolerable adverse side effects. The dosage unit includes an effective amount of a dopamine receptor agonist in combination with an intranasal carrier. The intranasal carrier includes a buffer. The buffer pH is selected to enhance absorption of the dopamine receptor agonist and to produce an erection within about 60 minutes of administering the dosage unit to a nasal mucosa of the mammal. Preferably, an erection is produced within about 45 minutes, more preferably within about 30 minutes, most preferably within about 15 minutes, and even further preferably in less than about 15 minutes.

The intranasal carrier of the intranasal dosage unit is preferably an aqueous solution. Further, the aqueous solution can be selected from the group including aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof.

Alternatively, the intranasal carrier of the intranasal dosage unit is a non-aqueous solution. The non-aqueous solution can be selected from a group including non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions and non-aqueous microemulsions and combinations thereof.

The intranasal carrier of the intranasal dosage unit can also be a combination of an aqueous solution and a non-aqueous solution.

Alternatively, the carrier of the intranasal dosage unit is a powder formulation. The powder formulation can be selected from a group including simple powder mixtures, powder microspheres, coated powder microspheres, liposomal dispersions and combinations thereof. Preferably, the powder formulation is powder

microspheres. The powder microspheres are preferably formed from various polysaccharides and celluloses selected from the group including starch, methylcellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, carbomer, alginate polyvinyl alcohol, acacia, chitosans and combinations thereof.

The intranasal dosage unit can also include an excipient having bio-adhesive properties. Preferably, the buffer of the intranasal dosage unit is selected to have a pH of from about 3 to about 10 and more preferably from about 3.5 to 7.0.

Preferably, the intranasal dosage unit includes a humectant. A humectant can be selected from the group consisting of soothing agents, membrane conditioners, sweeteners and combinations thereof.

The present invention also provides for a nasally administered pharmaceutical composition for treating male erectile dysfunction in a mammal including a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its solubility. The dopamine receptor agonist of this composition is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof. The system of this composition includes one of the following or combinations thereof: a glycol derivative; a sugar alcohol; glycerin; propylene glycol and glycerin; polyethylene glycol 400; ascorbic acid and water; sodium ascorbate and water; or sodium metabisulfite and water. Preferred glycol derivatives include propylene glycol and polyethylene glycol. Preferred sugar alcohols include mannitol and xylitol.

The present invention also provides for a nasally administered pharmaceutical composition for treating male erectile dysfunction in a mammal including a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its stability. The dopamine receptor agonist of this composition is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof. The system of this

composition includes one of the following or combinations thereof: a glycol derivative; a sugar alcohol; glycerin; propylene glycol and glycerin; polyethylene glycol 400; ascorbic acid and water; sodium ascorbate and water; or sodium metabisulfite and water. Preferred glycol derivatives include propylene glycol and polyethylene glycol. Preferred sugar alcohols include mannitol and xylitol.

These and other advantages of the present invention will be appreciated from the detailed description and examples which are set forth herein. The detailed description and examples enhance the understanding of the invention, but are not intended to limit the scope of the invention.

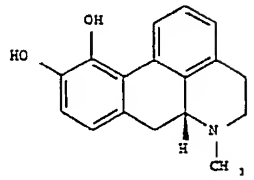
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compositions and methods for treating sexual dysfunction in a mammal. In particular, a method is provided for ameliorating male erectile dysfunction in a mammal by nasally administering to the mammal a therapeutically effective amount of a dopamine receptor agonist before, during or after sexual activity which is sufficient to induce an erection without causing substantial adverse side effects in the mammal.

For purposes of the present invention, the phrase "erectile dysfunction" is intended to encompass certain medically related symptoms resulting in the inability of a male to perform sexually, including penile dysfunction, as well as male impotence. As used herein, the term "impotence" is intended to mean the inability of a male to achieve and/or sustain a penile erection sufficient for vaginal penetration and intercourse.

As used herein, a "dopamine receptor agonist" is intended to encompass those members of the dopamine receptor agonist family which are able to ameliorate male erectile dysfunction when administered to a mammal. Apomorphine is an example of such a composition. Thus, the present invention is intended to encompass apomorphine and its functional equivalents including pharmaceutical salts and

chemically modified equivalents thereof, including for example pro-drug forms of apomorphine. Apomorphine can be represented by the formula:



and in the present invention can exist in a free base form or as an acid addition salt. For the purposes of the present invention, apomorphine hydrochloride is preferred; however, other pharmacologically acceptable moieties thereof can be utilized as well. The term "apomorphine" as used herein includes the free base form of this compound as well as pharmacologically acceptable acid addition salts thereof. In addition to the hydrochloride salt of apomorphine, other pharmacologically acceptable acid addition salts of apomorphine include the hydrobromide, the hydroiodide, the bisulfate, the phosphate, the acid phosphate, etc.

For the purposes of the present invention, apomorphine or a similarly acting dopamine receptor agonist is administered nasally in an amount sufficient to excite cells in the mid-brain region of the patient but without substantial adverse side effects.

This cell excitation is believed to be part of a cascade of stimulation that is likely to include neurotransmission with serotonin and oxytocin. Because dopamine receptors agonists act directly on regions of the mid-brain, the present invention also contemplates the use of such agonists for improving the sexual desire in both male and female mammals, as well as the amelioration of erectile dysfunction in males as set forth above.

The dopamine receptors in the mid-brain region of a patient can be stimulated to a degree sufficient to cause an erection by the nasal administration of apomorphine so as to maintain an adequate plasma concentration of apomorphine. The amount of

apomorphine nasally administered is an amount sufficient to cause an erection but is low enough not to cause substantial intolerable adverse side effects. As used herein, "substantial intolerable adverse side effects" include those effects caused by either the delivery system or the dopamine receptor agonist which are incompatible with the health of the user or which are so unpleasant as to discourage the continued use of the composition. Such effects include, for example, hypotension, nausea, vomiting, impaired vision, diaphoresis and ashen coloring.

Apomorphine is nasally administered about 30 to about 45 minutes prior to sexual activity, preferably about 15 to about 20 minutes prior to sexual activity, and more preferably less than 15 minutes prior to sexual activity.

The compositions according to the present invention can be administered, for example, as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of a composition can also include using a nasal tampon or a nasal sponge containing a composition of the present invention.

The dopamine receptor agonist can also be brought into a viscous basis via systems conventionally used, for example, natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the present compositions, many other excipients known in the art can be added such as preservatives, surfactants, co-solvents, adhesives, antioxidants, buffers, viscosity enhancing agents and agents to adjust the pH and the osmolarity.

The amount of dopamine receptor agonist administered to a patient will vary according to the delivery system used, and the age and weight of the patient. There are two critical parameters for selecting the appropriate dosage levels of the dopamine receptor agonist. First, the dosage level must be effective for achieving an erection in the patient and second, the dosage level must not cause substantial intolerable adverse side effects to the patient.

The onset of substantial intolerable adverse side effects, for example, nausea and/or vomiting, can be obviated or delayed by nasally delivering a dopamine receptor agonist at a controlled dissolution rate so as to provide circulating serum levels and mid-brain tissue levels of the dopamine receptor agonist sufficient for an erection and without inducing nausea and/or vomiting. When it is necessary to administer higher doses of a dopamine receptor agonist, for example, doses above about 2 mg, the likelihood of a substantial intolerable adverse side effect onset can be reduced by concurrently administering a ganglionic agent capable of inhibiting the ganglionic response, for example, nicotine or lobeline sulfate.

Other antiemetic agents that can be used in accordance with the present invention include metoclopramide; phenothiazines such as chlorpromazine, prochlorperazine, pipamazine, thiethylperazine and oxypendyl hydrochloride; serotonin (5-hydroxytryptamine or 5-HT) agonists such as domperidone, odansetron and histamine antagonists including buclizine hydrochloride, cyclizine hydrochloride and dimenhydrinate; parasympathetic depressants such as scopolamine; metopimazine; trimethobenzamide; benzquinamine hydrochloride; and diphenidol hydrochloride.

As set forth previously, the nasal delivery systems that can be used with the present invention can take various forms including aqueous solutions, non-aqueous solutions and combinations thereof. Aqueous solutions include, for example, aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous solutions include, for example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

The various forms of the delivery system set forth above can include a buffer to maintain the pH of the dopamine receptor agonist, a pharmaceutically acceptable thickening agent and a humectant. Desirably, the pH of the buffer is selected to

maintain the dopamine receptor agonist in a non-ionized form. In particular, the pH of the buffer is selected to optimize the absorption of the dopamine receptor agonist across the nasal mucosa. The particular pH of the buffer, of course, can vary depending upon the particular nasal delivery formulation as well as the specific dopamine receptor agonist composition selected. Buffers that are suitable for use in the present invention include acetate, citrate, prolamine, carbonate and phosphate buffers.

With respect to the non-aqueous formulations set forth above, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa.

In the present invention, the pH of the compositions should be maintained from about 3.0 to about 10.0. Compositions having a pH of less than about 3.0 or greater than about 10.0 can increase the risk of irritating the nasal mucosa of a recipient. Further, it is preferable that the pH of the compositions be maintained from about 3.0 to about 7.0.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be used in accordance with the present invention include methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation discussed above.

The compositions of the present invention can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used in the present invention include sorbitol, mineral

oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and combinations thereof. The concentration of the humectant in the present compositions will vary depending upon the agent selected.

In the present invention, other optional ingredients can also be incorporated into the nasal delivery system provided that they do not interfere with the action of the dopamine receptor agonist or significantly decrease the absorption of the dopamine receptor agonist across the nasal mucosa. Such ingredients include pharmaceutically acceptable excipients and preservatives.

To extend shelf life, preservatives can be added to the present compositions. Suitable preservatives that can be used with the present compositions include benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium chloride and preferably benzalkonium chloride is used. Typically, the preservative will be present in a composition in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

The present invention provides for the compositions as described above which are administered nasally to a mammal to treat erectile dysfunction. For purposes of the present invention, "administered nasally" or "nasal administration" is intended to mean that the dopamine receptor agonists are combined with a suitable delivery system for absorption across the nasal mucosa of a mammal, preferably, a human.

A preferred embodiment of the present invention provides for a nasally administered pharmaceutical composition that includes a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain the pH of the agonist, a pharmaceutically acceptable thickening agent and a humectant. As used herein, "therapeutically effective amount" means a unit dosage of the present dopamine receptor agonist which is able to be combined with a pharmaceutically acceptable nasal delivery system and absorbed through the nasal mucosa of a mammal

to produce an erection in about 1 hour, preferably in about 45 minutes, more preferably in about 30 minutes, and most preferably in 15 minutes or less which renders the intended physiological effect which is to induce a penile erection in a mammal with penile erectile dysfunction without causing substantial intolerable adverse side effects to the mammal. Preferably, the dopamine receptor agonist is selected from a group including apomorphine, chemically modified equivalents which include a pro-drug and pharmaceutical salts thereof.

Another preferred embodiment of the present invention provides for a method of treating impotence and male erectile dysfunction in a human in need of such a treatment. This method includes administering into a nasal cavity of a mammal for absorption through the nasal mucosa thereof a therapeutically effective dosage of a dopamine receptor agonist as previously set forth in combination with a nasal delivery system. The dopamine receptor agonist is preferably selected from a group including apomorphine, chemically modified equivalents which include a pro-drug and pharmaceutical salts thereof. For purposes of the present invention, the nasal delivery system can include a pharmaceutically acceptable buffer, a thickening agent and a humectant.

In another preferred embodiment of the present invention, a method is provided for administering a therapeutically effective amount of a dopamine receptor agonist to a mammal through a nasal membrane without causing substantial intolerable adverse side effects in the mammal. This method includes delivering to a nasal membrane of a mammal a dopamine receptor agonist which is dispersed in a nasal delivery system that includes a pharmaceutically acceptable buffer, a thickening agent and a humectant. In this method, the dopamine receptor agonist is effective for the treatment of a sexual dysfunction in a mammal, particularly impotence and/or erectile dysfunction in a male mammal.

Another preferred embodiment of the present invention provides for an intranasal dosage unit for treating impotency in a mammal and which does not cause

substantial intolerable adverse side effects in the mammal. The intranasal dosage unit includes an effective amount of a dopamine receptor agonist in combination with a pharmaceutically acceptable intranasal carrier. This carrier includes a buffer. The pH of the buffer is selected as set forth above to facilitate dopamine receptor agonist absorption through the nasal mucosa so an erection is achieved in about 60 minutes, preferably in about 45 minutes, more preferably in about 30 minutes and most preferably in 15 minutes or less after administration.

The following examples are provided to assist in further understanding the invention. The particular materials and conditions employed are intended to be further illustrative of the invention and are not limiting upon the reasonable scope thereof.

A series of experiments were performed to illustrate features and advantages of the present invention. Several conditions were common to each experiment. For example, in Examples 1-4, apomorphine was administered to healthy male subjects who did not suffer from erectile dysfunction. Further, none of the subjects took any medication for two weeks prior to these experiments.

The following examples show that apomorphine can be nasally administered without causing substantial intolerable adverse effects. A different dosage of apomorphine was administered in each experiment to determine a preferred range of dosages having minimal adverse effects.

EXAMPLE 1

TABLE 1 shows the results of an experiment in which 1.0 mg of apomorphine HCL was nasally administered to nine male subjects.

TABLE 1

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or of very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Nasal Burning	2	0	0	0	0	2
Sneezing	1	0	1	0	0	2
Unusual Taste	2	0	0	0	0	2
Nausea	1	1	0	0	0	2
Tearing of Eyes	1	0	0	0	0	1
Lightheadedness	1	0	0	0	0	1
Tiredness	3	0	0	0	0	3
Congestion	1	0	0	0	0	1
Sweating	1	0	0	0	0	1

It should be noted that some of the subjects of this experiment suffered from more than one symptom and one subject did not suffer from any symptoms.

As shown in TABLE 1, the symptoms suffered by the subjects in this experiment were generally not troublesome and of very short duration. One subject, though, suffered from moderate sneezing and another subject suffered from mild to moderate nausea. The adverse effects with nasal administration of 1.0 mg of

apomorphine HCL were minimal and the severity of the adverse effects were generally not troublesome.

EXAMPLE 2

TABLE 2 shows the results of an experiment in which 0.5 mg of apomorphine HCL was nasally administered to three male subjects.

TABLE 2

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE OF SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or of very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Nasal Burning	2	0	0	0	0	2
Nasal Pain	1	0	0	0	0	1
Unusual Taste	1	0	0	0	0	1

One of the subjects of this experiment did not suffer any symptoms and two of the three subjects in this experiment suffered mild symptoms which were not troublesome and were of very short duration. The results of this experiment show minimal adverse effects with nasal administration of 0.5 mg of apomorphine HCL.

The results of this experiment also show that nasal administration of apomorphine HCL was effective for inducing an erection. In particular, one of the three subjects experienced an erection while another felt the beginning of an erection.

EXAMPLE 3

TABLE 3 shows the results of an experiment in which 2.0 mg of apomorphine HCL was nasally administered to nine male subjects.

TABLE 3

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE OF SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or of very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Nasal Burning	1	0	0	0	0	1
Sneezing	0	1	0	0	0	1
Unusual Taste	4	0	0	0	0	4
Nausea	3	0	0	0	0	3
Lightheadedness	2	0	0	0	0	2

It should be noted that some of the subjects of this experiment suffered from more than one symptom and one subject did not suffer from any symptoms.

Eight of the nine subjects in this experiment suffered from symptoms of mild degree as shown in TABLE 3. Further, the symptoms suffered by all of the subjects were not troublesome. The results of this experiment show very minimal adverse effects with nasal administration of 2.0 mg of apomorphine HCL.

The results of this experiment also show that nasal administration of apomorphine HCL was effective for inducing an erection. In particular, three of the nine subjects of this experiment had a partial erection while one subject felt an erection.

EXAMPLE 4

TABLE 4 shows the results of an experiment in which 4.0 mg of apomorphine HCL was nasally administered to two male subjects.

TABLE 4

SYMPTOMS EXPERIENCED	NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS GIVEN BY THE DEGREE OF SEVERITY OF THE SYMPTOM					TOTAL NUMBER OF SUBJECTS EXPERIENCING SYMPTOMS
	Mild, not troublesome, or or very short duration	Mild to moderate, not troublesome, of short duration	Moderate, somewhat troublesome, or persistent	Moderate, somewhat severe, troublesome, or persistent	Severe, extremely troublesome, or constantly present	
Sneezing	0	0	0	1	0	1
Nausea	0	1	0	0	0	1
Lightheadedness	0	1	0	0	0	1

One subject of this experiment did not suffer any symptoms while the other subject experienced mild to moderate nausea and lightheadedness, which were not troublesome and were of very short duration, and moderate sneezing, which was somewhat troublesome. In particular, this subject felt like vomiting, felt lightheaded for twenty minutes after apomorphine was administered and sneezed four times. It is known in the art that the emetic effect of high dosages of apomorphine includes vomiting and therefore, it is believed that this subject suffered these symptoms due to the higher dosage of apomorphine.

The results of this experiment do not show substantial adverse effects with nasal administration of 4.0 mg of apomorphine HCL.

Examples 1-4 show that apomorphine can be nasally administered at different dosages without substantial adverse effects and further, adverse effects are minimal with a dosage of apomorphine of equal to or less than 2.0 mg.

EXAMPLE 5

TABLE 5 shows the solubility and stability of apomorphine hydrochloride dispersed in several different systems.

TABLE 5

System #	Composition of System	pH	Solubility (mg/mL)	Solubility Enhancement %	Improved Stability *
1	Water	3.6	20.9	-	-
2	Propylene Glycol	--	84.5	304.3	Yes
3	Glycerin	--	37.4	78.9	Yes
4	50% Propylene Glycol + 50% Glycerin	--	67.9	224.9	Yes
5	Polyethylene Glycol 400	--	19.9	None	Yes
6	1.8% Ascorbic Acid + 98.2% Water	2.3	25.0 - 30.0	19.6 - 43.5	Yes
7	0.2% Sodium Ascorbate + 99.8% Water	5.0	20.0 - 25.0	0 - 19.6	Yes
8	0.5% Sodium Metabisulfite + 99.5% Water	3.1	249	19.1	Yes

* Based on color change.

TABLE 5 shows the composition of several systems in which apomorphine HCL has been dispersed. System #1 includes water and served as a control for comparison with System #2 - System #8. TABLE 5 also shows the solubility of apomorphine HCL after it has been dispersed in the above systems. It also shows that the stability of apomorphine HCL has been improved after it has been dispersed in the above systems. The improved stability of apomorphine HCL was determined based on the color change of apomorphine HCL. For instance, a reduced degree of color

formation after dispersion of apomorphine HCL in a system would signify improved stability.

As shown in TABLE 5, the solubility of apomorphine HCL clearly improves significantly when it is dispersed in the compositions of System #2 - System #4. Further, the solubility of apomorphine HCL improved moderately when it was dispersed in the compositions of System #6 - System #8.

Apomorphine HCL exhibited improved stability when dispersed in each of System #2 - System #8.

The results of this experiment demonstrate that a pharmaceutical composition according to the present invention and including apomorphine dispersed in different systems as shown above, can improve the solubility and stability of apomorphine.

Thus, while there have been described what are presently believed to be the preferred embodiments of the present invention, those skilled in the art will realize that other and further embodiments can be made without departing from the spirit and scope of the invention, and it is intended to include all such further modifications and changes as come within the true scope of the claims set forth herein.

WHAT IS CLAIMED IS:

1. A method of ameliorating male erectile dysfunction in a mammal comprising nasally administering a therapeutically effective amount of a dopamine receptor agonist to said mammal before, during or after sexual activity which is sufficient to induce an erection without causing substantial intolerable adverse side effects to said mammal.

2. The method of Claim 1, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

3. A pharmaceutical composition for treating sexual dysfunction in a mammal comprising a therapeutically effective amount of a dopamine receptor agonist in combination with a nasal delivery system, wherein said pharmaceutical composition does not cause substantial intolerable adverse side effects in said mammal.

4. The pharmaceutical composition of Claim 3, wherein said dopamine receptor agonist is apomorphine.

5. The pharmaceutical composition of Claim 4, wherein said apomorphine is dispersed in an aqueous or non-aqueous formulation.

6. The pharmaceutical composition of Claim 4, wherein said nasal delivery system comprises a buffer to maintain the pH of said dopamine receptor agonist, a pharmaceutically acceptable thickening agent and a humectant.

7. The pharmaceutical composition of Claim 6, further comprising one or more pharmaceutical excipients.

8. The pharmaceutical composition of Claim 7, further comprising a pharmaceutically acceptable preservative.

9. The pharmaceutical composition of Claim 6, wherein said buffer is selected from the group consisting of acetate, citrate, prolamine, carbonate and phosphate buffers.

10. The pharmaceutical composition of Claim 6, wherein said thickening agent is selected from the group consisting of methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

11. The pharmaceutical composition of Claim 6, wherein said humectant is selected from the group consisting of sorbitol, glycerol, mineral oil, vegetable oil and combinations thereof.

12. A method of treating erectile dysfunction in a male mammal comprising nasally administering the composition according to Claim 3.

13. The pharmaceutical composition of Claim 3, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

14. The pharmaceutical composition of Claim 13, wherein said chemically modified equivalents comprise a pro-drug.

15. A nasally administered pharmaceutical composition comprising a therapeutically effective amount of a dopamine receptor agonist dispersed in a buffer to maintain its pH, a pharmaceutically acceptable thickening agent and a humectant, wherein said nasally administered pharmaceutical composition does not cause substantial intolerable adverse side effects when administered to said mammal.

16. The nasally administered pharmaceutical composition of Claim 15, wherein said dopamine receptor agonist is selected from the group including apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

17. The nasally administered pharmaceutical composition of Claim 16, wherein said chemically modified equivalents comprise a pro-drug.

18. A method of treating impotence and male erectile dysfunction in a human in need of such treatment comprising administering to a nasal membrane of said human an effective amount of a composition according to Claim 15.

19. A method of treating sexual dysfunction without causing substantial intolerable adverse side effects in a mammal comprising administering into a nasal cavity of said mammal a therapeutically effective dosage of a dopamine receptor agonist in combination with a nasal delivery system comprising a pharmaceutically acceptable buffer, a thickening agent and a humectant.

20. The method of Claim 19, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

21. The method of Claim 20, wherein said chemically modified equivalents comprise a pro-drug.

22. A method of administering a therapeutically effective amount of a dopamine receptor agonist to a mammal through a nasal membrane thereof comprising delivering to said nasal membrane a therapeutically effective amount of said dopamine receptor agonist which does not cause substantial intolerable adverse side effects in said mammal, wherein said dopamine receptor agonist is dispersed in a nasal delivery system comprising a pharmaceutically acceptable a buffer, a thickening agent and a humectant.

23. The method of Claim 22, wherein said dopamine receptor agonist is effective for the treatment of male erectile dysfunction in a mammal.

24. An intranasal dosage unit for treating impotency or erectile dysfunction in a mammal comprising an effective amount of a dopamine receptor agonist in combination with an intranasal carrier comprising a buffer, wherein said dosage unit does not cause substantial intolerable adverse side effects in said mammal and an erection is produced in said mammal within about 60 minutes of administering said dosage unit to a nasal mucosa of said mammal.

25. The intranasal dosage unit of Claim 24, wherein said erection is produced within about 45 minutes.

26. The intranasal dosage unit of Claim 24, wherein said erection is produced within about 30 minutes.

27. The intranasal dosage unit of Claim 24, wherein said erection is produced within about 15 minutes.

28. The intranasal dosage unit of Claim 24, wherein said erection is produced in less than about 15 minutes.

29. The intranasal dosage unit of Claim 24, wherein said intranasal carrier is an aqueous solution.

30. The intranasal dosage unit of Claim 29, wherein said aqueous solution is selected from the group consisting of aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof.

31. The intranasal dosage unit of Claim 24, wherein said intranasal carrier is a non-aqueous solution.

32. The intranasal dosage unit of Claim 31, wherein said non-aqueous solution is selected from the group consisting of non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

33. The intranasal dosage unit of Claim 24, wherein said intranasal carrier is a powder formulation.

34. The intranasal dosage unit of Claim 33, wherein said powder formulation is selected from the group consisting of simple powder mixtures, powder microspheres, coated powder microspheres, ribosomes and combinations thereof.

35. The intranasal dosage unit of Claim 24, further comprising an excipient having bio-adhesive properties.

36. The intranasal dosage unit of Claim 24, wherein said buffer is selected to have a pH of from about 3 to about 10.

37. The intranasal dosage unit of Claim 24, further comprising a humectant.

38. The intranasal dosage unit of Claim 37, wherein said humectant is selected from the group consisting of soothing agents, membrane conditioners, sweeteners and combinations thereof.

39. A nasally administered pharmaceutical composition for treating sexual dysfunction in a mammal comprising a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its solubility.

40. The nasally administered pharmaceutical composition of Claim 39, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

41. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises glycerin.

42. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises a glycol derivative.

43. The nasally administered pharmaceutical composition of Claim 42, wherein said glycol derivative is propylene glycol.

44. The nasally administered pharmaceutical composition of Claim 42, wherein said glycol derivative is polyethylene glycol.

45. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises a sugar alcohol.

46. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises propylene glycol and glycerin.

47. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises ascorbic acid and water.

48. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises sodium ascorbate and water.

49. The nasally administered pharmaceutical composition of Claim 39, wherein said system comprises sodium metabisulfite and water.

50. A nasally administered pharmaceutical composition for treating sexual dysfunction in a mammal comprising a therapeutically effective amount of a dopamine receptor agonist which has been dispersed in a system to improve its stability.

51. The nasally administered pharmaceutical composition of Claim 50, wherein said dopamine receptor agonist is selected from the group consisting of apomorphine, chemically modified equivalents and pharmaceutical salts thereof.

52. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises glycerin.

53. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises a glycol derivative.

54. The nasally administered pharmaceutical composition of Claim 53, wherein said glycol derivative is propylene glycol.

55. The nasally administered pharmaceutical composition of Claim 53, wherein said glycol derivative is polyethylene glycol.

56. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises a sugar alcohol.

57. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises propylene glycol and glycerin.

58. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises polyethylene glycol 400.

59. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises ascorbic acid and water.

60. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises sodium ascorbate and water.

61. The nasally administered pharmaceutical composition of Claim 50, wherein said system comprises sodium metabisulfite and water.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04268

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/44
US CL : 514/284
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/284

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, CAPLUS, BIOSIS
search terms: apomorphine, nasal, erectile, dopamine, buffer.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,756,483 A (MERKUS) 26 May 1998, entire document.	1-61
Y	US 5,770,606 A (EL-RASHIDY et al.) 23 June 1998, entire document	1-61
Y	WO 99/27905 A (DANBIOSYST UK LIMITED) 10 June 1999, entire document	1-61
Y,P	WO 99/66933 A (NEW MILLENNIUM PHARMACEUTICAL RESEARCH INC.) 29 December 1999, entire document	1-61

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 MAY 2000	12 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Shengjun Wang Telephone No. (703) 308-1235

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